UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)**

PLAINTIFFS' REPLY BRIEF IN SUPPORT OF *DAUBERT* MOTION TO PRECLUDE OPINIONS OF DEFENSE EXPERT ALI AFNAN, PH.D.

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ARGUMENT

I.

DR. AFNAN CANNOT PROVIDE CHEMISTRY OR TOXICOLOGY OPINIONS

Defendants incredibly argue to allow Dr. Afnan to offer chemistry and toxicology opinions that he said he could not and would not provide at his deposition. (*See* Pls.' Initial Br. 3). The thrust of the argument is that Dr. Afnan has training and education in chemistry, but that is not enough when the expert and the counsel defending his deposition made clear that he was only offered as an expert in cGMPs and disclaimed him having any expert opinions in chemistry. The deposition testimony was very clear, and followed from the clear statement in his report that he deferred to Dr. Xue in that area. (Afnan R. 55-56 (Ex. 13)).[1] It would be unfairly prejudicial to allow Dr. Afnan's refusals to answer chemistry questions, and his counsel's statements that he was not offered as a chemistry expert at his deposition, to be superseded at this point.

Defendants tack on the argument that Plaintiffs failed to point to a specific opinion that should be excluded. First, exclusion is not dependent on listing the exact phrasing of each of the specific opinions the expert cannot give; it is enough to exclude an entire subject area. In addition, notwithstanding Defendants' argument, Plaintiffs' initial brief does point to specific testimony to make those points. The motion is illustrated with examples of technical chemistry questions Dr. Afnan could not answer and/or his defending attorney objected to as outside the scope of his expertise during his deposition. (*See* Pls.' Initial Br. 3). Defendants' argument also presents a good example of the type of question he should be barred from answering at trial, interpreting the chemistry literature with regard to whether ZHP's scientists had "a reasonable scientific basis to

[1] Unless otherwise noted, exhibits are attached to the initial certification in support of this motion, except for Exhibits 33 through 39, which are attached to the certification in support of this reply.

expect that NDMA or NDEA could form." (Defs.' Br. 21-22).

There is nothing difficult about this routine motion. The Court's Order should preclude Dr. Afnan from providing chemistry opinions. Additionally, to the extent Dr. Xue's opinions are excluded, Dr. Afnan's opinions relying on Dr. Xue should also be excluded.

II.

DESCRIBING DR. AFNAN AS A REBUTTAL EXPERT DOES NOT CURE THE METHODOLOGICAL INSUFFICIENCY UNDERLYING HIS OPINIONS

Defendants have confirmed that Dr. Afnan is not offering any affirmative opinions, and has been offered solely as a rebuttal expert "to critique the opinions offered by" Plaintiffs' experts. (Defs.' Br. 1, 5). In other words, he was retained to "opine on the subjects which are - - or the topics which are raised against ZHP." (Dr. Afnan Dep. Tr. 138:6-14 (Ex. 1)). Thus, the starting point is that his potential testimony must be sharply limited to this narrow role, and he cannot offer affirmative opinions or opinions that are not directly responsive to Plaintiffs' experts' affirmative opinions—to the extent any of the opinions is/are found to be reliable.

Defendants admit that Dr. Afnan "did not independently evaluate ZHP's application of cGMPs…in the development and use of its manufacturing processes." (Defs.' Br. 6). Therefore, they admit that he did not assess the very issue he is ostensibly responding to. How can he be permitted to opine on a topic he did not reliably consider? This presents a significant hurdle to the expert being permitted to opine on this subject. Whether the expert is offering affirmative or "rebuttal" opinions, he still needs to be able to demonstrate the qualifications and methodological validity necessary to provide a reliable opinion.

The premise of Defendants' arguments is that a rebuttal expert need not demonstrate methodological validity for his opinions, as if tagging an expert as a rebuttal expert peels away the rules that apply to any opinion the jury will hear. This is incorrect. Whether the opinion is an

affirmative opinion, or is couched as rebuttal, the fact remains that the expert intends to offer opinions, which are subject to *Daubert*. *See, e.g.*, Rule 702 (making no distinction between which party proffers the expert); *Montgomery County v. Microvote Corp.*, 320 F.3d 440, 447-49 (3d Cir. 2003) (excluding the defense expert after reciting the standard *Daubert* analysis, explaining "the data underlying [the defense expert's] opinion was so unreliable that no reasonable expert could base an opinion on it"); *United States v. Ancient Coin Collectors Guild*, 899 F.3d 295, 318-19 (2018) (same); *Decker v. GE Healthcare Inc.*, 770 F.3d 378, 394 (6th Cir. 2014) (same).

ZHP cites a single Third Circuit case for the proposition that defense experts responding to plaintiff experts' opinions somehow face a lower standard under *Daubert*. But *Holbrook v. Lykes Bros. S.S. Co.* focused on whether the defense expert had offered his opinion with the requisite "certainty" when the defendant did not bear the burden of proof on the issue. 80 F.3d 777, 785-86 (3d Cir. 1996). The Court held that the expert had "testified on this issue to a reasonable degree of medical certainty," explaining "[a]lthough that testimony would have been insufficient to prove that radiation exposure caused the cancer, a burden which the defense did not bear, it was sufficiently certain and could help the jury to evaluate testimony by plaintiff's experts that asbestos exposure caused the cancer, an issue on which plaintiff bore the burden of proof." *Id.* at 786. Plaintiffs' motion does not attack Dr. Afnan's opinions based on his stated level of certainty, so *Holbrook* is irrelevant to Plaintiffs' arguments concerning the reliability of Dr. Afnan's methodology, nor does that case establish a special standard for "rebuttal" experts. The other nonbinding trial court cases relied on by Defendants are equally irrelevant to Plaintiffs' attacks on Dr. Afnan's methodology.

III.

DR. AFNAN'S METHODOLOGY IS NOT RELIABLE

Defendants lean on the general statement in Dr. Afnan's report that he considered various sources of information. (Defs.' Br. 7). However, in his deposition, he admitted to significant methodological gaps in what he actually considered—including important documents and information that were discussed by Dr. Bain; thus, even in Defendants' view of Dr. Afnan as a rebuttal expert, his failure to match up and address what was relied on by the Plaintiffs' experts renders his opinions not a "fit" and unhelpful.

A. Dr. Afnan Admitted He Did Not Consider ZHP's Internal SOPs.

Defendants attempt to deflect Dr. Afnan's failure to consider ZHP's SOPs by mischaracterizing the questions he was asked at his deposition, and suggesting that he was asked to recite the list of standards applied by ZHP from memory. (Defs.' Br. 9). Dr. Afnan was asked to list "each standard that applied to ZHP's development and manufacture of valsartan with regard to cGMP… I want to know what - - the universe of what you believe applied to them that they had to adhere to is… Please list for me those cGMP standards, whether they are external to ZHP or internal to ZHP, such as standard operating procedures that applied to ZHP in its development and manufacture of valsartan. I need to know the list of what you believe they were required to comply with when they developed and manufactured the valsartan." He was not told he could not reference his report or any other document.[2] (Dr. Afnan Dep. Tr. 35:8-14, 37:16-38:1).

In response, Dr. Afnan pointed to ICH Q7, which he described as one of the "What do

[2] Plaintiffs agree that a deposition is not a memory test, nor is it a basis to exclude the expert if the expert misspeaks during a deposition. Unfortunately, ZHP's position is very different in its affirmative *Daubert* motions; for example, related to Dr. Susan Bain. Most important, that is not the thrust of this motion against Dr. Afnan.

do's," and unequivocally stated that he did not review ZHP's internal standards—which are the how-to-do's: "**Now, about the internal standards, that would be the list of ZHP's SOP's, which I do not have. That was beyond the scope of my agreement…I was not tasked with assessing all the GMPs of ZHP**." (*Id.* at 39:6-40:15). Dr. Afnan did not say he reviewed the internal SOPs and needed the list of what he reviewed to answer, but it was "not in front of him," as fancifully suggested by Defendants, contrary to the actual testimony (nor is such a list contained in or discussed in his report). Nor did he say that merely "**reciting** every single SOP" was beyond the scope of his assignment. (Defs.' Br. 9). And defense counsel did not come back to clarify or correct this testimony. His testimony was quite clear.

Defendants point out that despite his testimony, Dr. Afnan's report discussed one ZHP SOP, SMP-018 regarding change control for manufacturing process changes. The fact that a single SOP is discussed in the report does not necessarily mean Dr. Afnan evaluated it—he testified this is not something he was retained to do. But even if he did, contrary to his testimony, that is only one of the multiple SOPs relied on by Dr. Bain, and would be the most he could potentially address—as a "rebuttal" expert, if the discussion in the report were not also unreliable.[3]

[3] Dr. Afnan's discussion of SMP-018 is limited to the definition of "critical change" and how that definition somehow overlaps with the FDA's definition of "minor change," despite the FDA observing this discrepancy and including it as part of its first observed cGMP violation in 2018:

> [Y]ou do not have an adequate classification procedure for determining the level of testing, validation, and documentation needed to justify changes to a validated process. You do not consistently classify changes. You do not always increase testing, validation, and the documentation required to justify changes to a validated process based on the classification of a proposed change. Amendment to Drug Master File Valsartan USP (Process IT) DMF# 23491 dated December 10, 2013 indicates the amendment was submitted for minor changes for drug substance manufacturing. Amendment to Drug Master File Valsartan USP (Process DMF# 23491 contradicts your internal Change Request PCRC-11025 which lists change control classification as critical change.

Defendants are unable to point to any discussion in his report, or even a citation to two other important ZHP SOPs that Defendants admit were discussed by Dr. Bain in her report: the SOP titled "Guideline for Genotoxic Impurity Evaluation," and the SOP titled "Quality Risk Management." His report is entirely silent on those and all other internal SOPs, which were discussed in Dr. Bain's report. (Defs.' Br. 10; *see also* ZHP00000417 (English trans. of Ex. 17)). Thus, he did not address this issue either affirmatively or as a so-called rebuttal expert whose testimony can fit, as a response to Dr. Bain.

It was not for Plaintiffs' counsel to ask questions in the deposition and bring out opinions with regard to SOPs not even mentioned in the report and only referenced as documents cited in Dr. Bain's report (not even specifically listed in his unorganized chart of bates numbered documents without any additional description). Their complete absence in the report, plus Dr. Afnan's concession in his deposition that he did not consider the SOPs because "That was beyond the scope of my agreement," means that he did not incorporate them into his analysis. He cannot testify to whether ZHP satisfied cGMPs because he failed to consider and evaluate the cross-section of important cGMP sources that applied.

Dr. Afnan either had a flawed methodology since he did not consider those SOPs on the face of his report and testimony, or provide any analysis for how those SOPs fit into this case. Taking Defendants' rebuttal expert argument to its logical conclusion, his "rebuttal" methodology

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(PRINSTON000162370 (Ex 3)). In line with his purpose to fall in line with ZHP's insistence that it did nothing wrong, Dr. Afnan's report does not address this finding from the FDA but instead emphasizes ZHP's response to this observation that ZHP can classify changes however it wants internally and externally because "the FDA would have applied the same standards" "regardless of how ZHP described the manufacturing process change." (Afnan R. 60). Dr. Afnan is clearly wrong because the FDA would not have described ZHP's classification procedure as "inadequate" if classifying changes were as meaningless as he contends. This is not an issue of weight. It is a methodological flaw.

is flawed since he did not analyze in his report or in his testimony those important SOPs and related documents underpinning Dr. Bain's opinions. In either case his methodological basis to comment on the internal SOPs is too thin to be permitted.

B. Dr. Afnan's "Threshold" Opinion Is Methodologically Unsound

Defendants fail to grapple with the core problem in Dr. Afnan's opinion that ZHP acted appropriately because any impurity below 0.1% was presumptively acceptable, regardless of what the impurity was. This proposed opinion is objectively wrong as a factual matter. Their response completely ignores the key language in ICH Q3A and the 2008 FDA Guidance, which ZHP confirmed was applied by them and thus binding.[4] That language explicitly states that the threshold is **not applicable** to "unusually toxic substances," including NDMA and NDEA. (Pls.' Initial Br. 17-19). ZHP's **complete failure** to address the clear language of these controlling cGMP guidances in their opposition brief demonstrates that they have no substantive counter. The Court should explicitly note the invalidity of the application of the threshold theory to NDMA and NDEA, since it is explicitly inapplicable to NDMA and NDEA and thus methodologically invalid to apply under the facts here.

Instead of arguing the merits, Defendants fall back on the argument that this is a reasonable disagreement and thus a matter for cross-examination. They argue the methodologically invalid point made by Dr. Afnan in his deposition that the threshold applies unless you expect or know that an impurity to which the threshold is inapplicable is the cause. But that is incorrect, and illogical. The whole point is what a manufacturer must do to evaluate and identify **unknown**

[4] The suggestion that the 2008 FDA Guidance was a draft and non-binding and thus not of any moment is obviously completely wrong. As set forth in the moving brief, ZHP cited to that Guidance in the DMFs for the contaminating manufacturing processes, and 30(b)(6) witness Peng Dong admitted on behalf of ZHP that the Guidance was applied by ZHP. (Pls.' Initial Br. 20).

impurities. Thus, in addition to being an incorrect description of what the standards say, his opinion renders his entire analysis irrelevant to the situation here, where the impurities were unknown.

C. Dr. Afnan Did Not Address ZHP's Failure to Consider the Potential Introduction of Amines Via Commercially Purchased Solvents DMF and TEA.

Defendants admit that Dr. Afnan completely failed to consider the potential for the amines to have been introduced as impurities of the DMF and TEA utilized in the respective manufacturing processes. (Defs.' Br. 12). They fall back on the argument that as a rebuttal expert, he did not need to address this issue since he says it was not addressed by Plaintiffs' experts. Aside from the invalidity of Defendants' argument that "rebuttal" experts can provide methodologically unreliable opinions, that argument fails because this issue **was** raised by Plaintiffs' experts as well in as ZHP's Deviation Investigation Reports, which are cited and quoted by Plaintiffs' experts in their reports and depositions. (*See, e.g.*, Dr. Bain R. 9, 15, 20, 30, 35, 50, 60 (Ex. 33); Dr. Hecht 7/6/21 R. 20 (Ex. 34); Dr. Hecht 10/31/22 R. 2-3 (Ex. 35); PRINSTON0075854-56, 961 (Ex. 9)). And this was addressed in the depositions of both Dr. Hecht and Dr. Bain, which Dr. Afnan testified he was provided before his deposition, as recognized by Defendants in their motion.[5] For example, Dr. Hecht explained: "In fact, DMF sometimes has a fishy odor due to the dimethylamine. So, you know, dimethylamine is a potential contaminant of DMF, that's well-established." (Dr. Hecht 1/13/23 Dep. Tr. 52:24-53:5, 93:19-95:12 (emphasis added) (Ex. 36); Dr. Bain Dep. Tr. 236:15-237:11 (Ex. 37)). Defendants do not explain why Dr. Afnan was completely unaware of this issue in his deposition.

Defendants weakly try to salvage Dr. Afnan by pointing to conclusory testimony Dr. Afnan

[5] Defendants argue that the issue is whether Dr. Afnan's report presents an unreliable methodology, when the question is whether his report and/or his deposition testimony, where he had the opportunity to rely on everything he had been provided, together demonstrate a reliable methodology.

gave indicating that ZHP did what it was supposed to do. The problem with the cited testimony is that Dr. Afnan was providing a generic, non-responsive talking point in response to a question at his deposition as to whether ZHP was required "to assess the potential risks from the potential impurities that could be introduced to the valsartan manufacturing process." (Dr. Afnan Dep. Tr. 142:1-143:2). The question was repeated over and over, and rather than answer the question as to what ZHP was required to do, he continually said that ZHP did what it was supposed to do—with the encouragement of defense counsel—never providing any substantive basis for this conclusion. (Dr. Afnan Dep. Tr. 142:1-155:5). This evasion was not responsive, and does not cure the fact that he did not take this issue into account or offer any opinions on the issue.

Dr. Afnan did not address this issue at all, and cannot be permitted to do so at trial. His failure to consider this pathway to introduction of the amines that were nitrosated to create NDMA and NDEA dooms his opinions, even in rebuttal, because he failed to consider one of the two ways in which the amines could have been introduced to the processes. This is not a mere issue for cross-examination; it is a methodological gap.

D. Dr. Afnan's Consideration of FDA Documents.

Dr. Afnan's opinions are based in part on his assumption that the FDA Warning Letter to ZHP is of no import, calling it "informal and advisory" and "made in hindsight.' (Defs.' Br. 15). Those opinions are legally inaccurate and impermissible, and ZHP's experts cannot be permitted to negate the significance of the Warning Letter, as a matter of law. A Warning Letter is a significant FDA document:

> ***When FDA finds that a manufacturer has significantly violated FDA regulations*, FDA notifies the manufacturer. This notification is often in the form of a Warning Letter. The Warning Letter identifies the violation, such as poor manufacturing practices, problems with claims for what a product can do, or incorrect directions for use. The letter also makes clear that the company must correct the problem and provides directions and a timeframe**

> **for the company to inform FDA of its plans for correction. FDA then checks to ensure that the company's corrections are adequate.** Matters described in FDA warning letters may have been subject to subsequent interaction between FDA and the recipient of the letter that may have changed the regulatory status of the issues discussed in the letter.

FDA, *About Warning and Close-Out Letters* (emphasis added) (Ex. 38). The FDA's findings in the Warning Letter—that ZHP committed multiple cGMP violations, and that the API was consequently adulterated—cannot be denied or downplayed by Dr. Afnan. These are not matters of interpretation or potential scientific disagreement, they are facts. Moreover, his position that hindsight analysis of ZHP's misconduct is not valid is so obviously wrong that it is frivolous. These opinions are unsound, and cannot be presented to a jury as reliable expert testimony.

E. Dr. Afnan's Failure to Reliably Consider Damaging Evidence Against ZHP.

Dr. Afnan was unable to say whether he had seen ZHP's draft Deviation Investigation Report, in which ZHP admitted to the inadequate scientific analysis of the potential genotoxic impurities. (Pls'. Initial Br. 26). Defendants point to his reliance list, but do not deny it was ignored in Dr. Afnan's report.

Most important, Defendants ignore the biggest problem: **when asked to assume the statement is correct, he still asserted that it was irrelevant (with no basis).** How can such a central admission be irrelevant? Thus, he admitted that under his methodology, even if ZHP performed an inadequate scientific analysis in violation of cGMPs requiring an adequate scientific analysis, he would not opine that they failed to adhere to cGMPs. This is yet another example of his outcome driven approach to this case, yielding a conclusion with no basis in logic, fact, or law—and lacking methodological reliability.

F. Dr. Afnan's Testimony About USP Requirements Is Unreliable.

Defendants mischaracterize Dr. Afnan's testimony. He did not dispute the plain language

of the USP guidance requiring development of "additional tests and analytical methods if you change the process and you're going to introduce external sources that could bring impurities into the process." Rather, he admitted that is the language in the USP requiring all necessary testing to be done to ensure there are no unacceptable impurities, but stated (based on nothing in the USP) that this only applied "if you believe that there are undesirable impurities present. Q3A allows you to have less than .1 percent." (Dr. Afnan Dep. Tr. 390:3-19). Thus, he again retreated to his unsound conclusion that impurities need only be identified if the manufacturer already knows they are there. This made-up approach keyed to knowing the answer before the investigation is undertaken is completely illogical and not supported by any applicable guidance or standard, layered on the repeated resort to the inapplicable 0.1 threshold.

The crux of Defendants' argument is that Dr. Afnan should be allowed to testify that the USP permitted the NDMA and NDEA contamination. (Defs.' Br. 16-17). This opinion is absurd. It cannot be reconciled with the fact that the nitrosamines are not part of the approved formulation or impurity profile, and cannot be reconciled with Dr. Afnan's own concessions in the testimony preceding and after the testimony cited by Defendants that **this was not permitted**. (Dr. Afnan Dep. Tr. 386:14-389:8, 391:22-392:15). The USP did not permit the nitrosamine contamination to exist, as a matter of law, and Dr. Afnan cannot suggest to the contrary.

G. Dr. Afnan's Conclusions Are the Product of a Flawed Approach.

Defendants pretend that Dr. Afnan did not provide testimony that demonstrates his unreliable methodology, which was built on a weak foundation. For example, in addition to the above examples, they claim that Dr. Afnan's circular argument that ZHP was not expected to identify the nitrosamines because they did not do so, was actually just the product of a question from Plaintiffs' counsel. (Defs.' Br. 17, n.6). The transcript belies that argument. He clearly testified his opinion was based in part on: "They didn't see, they didn't predict – they didn't

predict, they didn't estimate, they did not come up with that expectation of, oh, NDMA will be formed here," and "So they looked at it; it was not there. They didn't see it. They did not know about NDMA or NDEA." (Dr. Afnan Dep. Tr. 360:18-361:1, 396:23-397:2). That is the point. Their failures cannot double as the justification for those failures.

CONCLUSION

Dr. Afnan's opinions are hopelessly flawed, from top to bottom. For the foregoing reasons, Ali Afnan, Ph.D should be precluded from offering any opinions in this case.

Respectfully,

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Dated: April 25, 2023

CERTIFICATE OF SERVICE

I hereby certify that on April 25, 2023, I electronically filed this brief and my supporting certification with the Clerk of the Court using CM/ECF system which will send notification of such filing to the CM/ECF participants registered to receive service in this MDL. In addition, I hereby certify that an unredacted copy of my supporting certification will be served contemporaneous to filing via email on the Court, Special Master, and the Defense Executive Committee at DECValsartan@btlaw.com, with the exception of the unredacted exhibits, which will be sent to the Court on a thumb drive via FedEx and to the Defense Executive Committee via a Dropbox link.

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Dated: April 25, 2023